Mapping Cortical and Subcortical Asymmetry in Obsessive-Compulsive Disorder: Findings from the ENIGMA Consortium

Abstract

Objective: Lateralized dysfunction has been suggested in Obsessive-Compulsive Disorder (OCD). However, it is currently unclear whether OCD is characterized by abnormal patterns of structural brain asymmetry. Here we carried out by far the largest study of brain structural asymmetry in OCD.

Method: We studied a collection of 16 pediatric datasets (501 OCD patients and 439 healthy controls), as well as 30 adult datasets (1777 patients and 1654 controls) from the OCD Working Group within the ENIGMA (Enhancing Neuro-Imaging Genetics through Meta-Analysis) consortium. Asymmetries of the volumes of subcortical structures, and of regional cortical thickness and surface area measures, were assessed based on T1-weighted MRI scans, using harmonized image analysis and quality control protocols. We investigated possible alterations of brain asymmetry in OCD patients. We also explored potential associations of asymmetry with specific aspects of the disorder and medication status.

Results: In the pediatric datasets, the largest case-control differences were observed for volume asymmetry of the thalamus (more leftward; Cohen’s $d = 0.19$) and the pallidum (less leftward; $d = -0.21$). Additional analyses suggested putative links between these asymmetry patterns and medication status, OCD severity, and/or anxiety and depression comorbidities. No significant case-control differences were found in the adult datasets.

Conclusions: The results suggest subtle changes of the average asymmetry of subcortical structures in pediatric OCD, which are not detectable in adults with the disorder. These findings may reflect altered neurodevelopmental processes in OCD.

Keywords
laterality; brain asymmetry; obsessive-compulsive disorder; thalamus; pallidum; mega-analysis

Introduction

Obsessive-Compulsive Disorder (OCD) is a psychiatric disorder with a lifetime prevalence of approximately 2% (1–4). OCD involves persistent, intrusive and unwanted thoughts
(obsessions) as well as repetitive behaviors which might be accompanied by mental acts (compulsions) (4). As a heterogeneous neuropsychiatric condition with considerable heritability of roughly 40% (5), OCD has significant genetic and non-genetic determinants (4), but the pathophysiology of this complex disorder remains unclear.

Left-right asymmetry is an important aspect of human brain organization for multiple functions (6). For example visual-spatial processing and emotions that elicit withdrawal behaviors are usually right-lateralized in healthy people (7–10), whereas language-related processes, hand motor dominance, and emotions that elicit approach behaviors tend to be left-lateralized in the brain (11, 12). Alterations of asymmetry have been reported in various psychiatric and neurocognitive conditions, including schizophrenia (13, 14), autism (15) and dyslexia (16). Altered functional laterality has also been investigated in OCD (17, 18), partly due to observations of psychometric deficits within the visual-spatial domain (19–21), as well as altered emotional processing (22–25). For example, a behavioral study found reduced functional asymmetry for spatial attention in OCD patients, and also that less typical asymmetry was correlated with more serious obsessions (20). Several studies found greater impairment in visual-spatial memory compared with verbal memory in OCD, suggestive of right-sided dysfunction (17, 18, 26). Increased left-right asymmetry of electroencephalographic (EEG) activity at rest, or reduced activity in the right hemisphere linked to approach/avoidance motivation, has also been reported in OCD compared to healthy controls (19, 22). However, left-sided dysfunction has also been suggested in OCD, on the basis of neuropsychological data (23) as well as neuroimaging studies (27–29).

Importantly, any structural basis linked to altered functional laterality in OCD is still unclear. Two previous studies explored brain structural asymmetry in OCD as a specific outcome of interest, but with low sample sizes. In one of these studies, with 16 OCD patients, leftward asymmetry (i.e., left > right) of cortical thickness in the anterior cingulate region was found in OCD patients and their siblings but not in matched controls, and this was claimed to present a potential endophenotype linked to increased hereditary risk for OCD (34). In the other study, with 32 patients, significant differences of frontal white matter volume asymmetry were found in both medicated (N= 19) and non-medicated (N= 13) patients, as compared with healthy controls (35). Unfortunately, small sample sizes tend to limit the reliability of findings in human neuroscience (36), and the extent of any association between OCD and structural brain asymmetry remains uncertain.

The OCD working group within the Enhancing Neuro-Imaging Genetics through Meta-Analysis (ENIGMA) consortium (37) recently achieved more highly powered analyses of
brain changes in OCD, based on a sample size of over 1500 OCD individuals and a similar number of controls (38). They reported several regional case-control differences in cerebral cortical measures which involved only one hemisphere (38). However, these analyses did not examine whether effect sizes were significantly different on the left and right sides, and asymmetry was not quantitatively characterized. Unilateral patterns in this and other studies may arise from small but uniform bilateral effect sizes; the fact that statistical significance was achieved on one side, but not on the other, does not necessarily indicate a significant change in asymmetry. Furthermore, a post-hoc statistical comparison of the left and right-sided effect sizes as reported by the previous ENIGMA study (38) would not yield the same level of statistical power as can be provided by utilizing the individual-level, paired left and right data, to analyze asymmetry alterations in OCD. In addition, a previous ENIGMA study of subcortical volumes in OCD only reported combined left and right volumes (39).

Here, we used the latest data for both subcortical and cortical structures from the ENIGMA OCD Working Group, and targeted hemispheric structural asymmetry across subcortical and cortical measures, as assessed by subject-specific asymmetry indexes, $AI = (\text{Left} - \text{Right}) / ((\text{Left} + \text{Right})/2)$ (40). The AI is a widely used approach in studies of brain asymmetry (e.g., (41, 42)). Our primary interest was to compare structural asymmetries between patients and healthy controls, but we also performed post-hoc analyses to investigate possible associations of brain asymmetries with medication status, age at disease onset, disease duration, OCD severity, and presence of anxiety and depression comorbidities. As the recent studies from the ENIGMA OCD working group had indicated distinct alterations in pediatric and adult patients (38, 39), and because asymmetries of both cortical and subcortical structures are also known to change subtly with age in the healthy population (40, 43), we carried out all analyses for the pediatric (<18 year old) and adult (>=18 year old) data separately (see also (44)).

**Materials and Methods**

See Supplementary Materials for detailed methods.

**Datasets.**

The datasets used in this study were provided by members of the OCD Working Group within the ENIGMA Consortium (37). There were 46 independent datasets from 16 countries: 16 pediatric datasets comprising 501 OCD patients and 439 healthy controls, and 30 adult datasets comprising 1777 OCD patients and 1654 healthy controls (Table 1, Figure S1–2 and Table S1). All local institutional reviews boards permitted the use of extracted measures from their anonymized data. In addition, we leveraged publicly available summary statistics which describe the average form of brain regional asymmetries, based on our previous larger studies of healthy individuals (40, 43).

**Image Acquisition and Processing.**

Structural T1-weighted MRI scans were acquired and processed locally at each collection site. Images were acquired at different field strengths (1.5 T and 3T). All images were analyzed using one automated and validated pipeline, i.e. “recon-all” as implemented in
FreeSurfer. For each subject, surface area and mean thickness was extracted for each of the 68 cortical regions (34 per hemisphere) in the Desikan-Killiany parcellation scheme (45), as well as total hemispheric surface area, and the average mean thickness over each hemisphere. In addition, volumes of eight subcortical regions of interest, including seven subcortical structures (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus), and the lateral ventricle volume, were calculated.

Asymmetry indexes.
The aim of this study was to investigate differences in subcortical and cortical asymmetry related to OCD. To this end, for each participant, and each subcortical or cortical measure, an Asymmetry Index (AI) was defined as \( \frac{(L-R)}{(L+R)/2} \), where L and R represent the corresponding left and right volume measures (from subcortical regions), or thickness and surface area measures (from cortical regions). This AI formula has been widely used in previous brain asymmetry studies (41, 42, 46), including our own (8, 40, 43).

Case-control analyses.
Separately for the pediatric and adult data, and for each AI, we pooled data from all available individuals from each dataset, and used a mega-analytical framework to investigate the case-control effects. Specifically, for each AI, we used a linear mixed-effect model (using *lme4* R package), with AI as the outcome variable, and a binary indicator of diagnosis (0=controls, 1=OCD patients) as the predictor of interest. In each model, a binary variable for sex, and a continuous measure for age (in years at time of scan) were included as confounding factors, and the categorical variable ‘dataset’ as a random-effect term.

Separately for thickness and surface area, we additionally calculated an overall ‘typicality score’ per subject, which indexed how much a given subject deviated from the population mean asymmetry profile, when considered simultaneously across all 34 cortical regions. A lower typicality score indicates more deviation from the mean asymmetry profile in the population.

OCD case-only analyses of clinical characteristics.
For AIs which were potentially associated with OCD in the main analysis (see Results), we further investigated, within cases only, whether the AIs were associated with specific aspects of the disorder and medication status.

Results
An overview of the datasets is provided in Table 1, Figure S1–2, and Table S1.

Pediatric data.
The results for both subcortical and cortical AIs in the pediatric data, including the effect size estimates for diagnosis on each AI, are presented in Figure 1 and Tables S2–S4.

The largest effects of diagnosis in pediatric cases were more leftward asymmetry of the thalamus \( (t = 2.84, p = 0.0047, d = 0.19; \text{Figure 1–2}) \), and less leftward asymmetry of the
pallidum volume \((t = -3.17, p = 0.0016, d = -0.21; \text{Figure 1–2})\). These two findings were significant when controlling the FDR at 0.05 (see Materials and Methods). Post hoc analyses showed that these case-control differences were mainly due to a left thalamus which was relatively larger in OCD patients than controls (Left: \(t = 4.08, p = 4.89 \times 10^{-5}, d = 0.27\); Right: \(t = 2.12, p = 0.034, d = 0.14\)), and a left pallidum which was relatively smaller in OCD patients than controls (Left: \(t = -1.98, p = 0.048, d = -0.13\); Right: \(t < 1.0, p = 0.35, d = 0.062\)) (see also Figure 2B for distribution and group differences of each unilateral volume measure). In addition, we confirmed that the effects remained when excluding possible outliers in each AI per dataset (see Methods) (pediatric thalamus volume asymmetry: \(t = 2.90, p = 0.0038, d = 0.19\); pediatric pallidum volume asymmetry: \(t = -3.16, p = 0.0016, d = -0.21\)).

Within pediatric patients only, there were no differences of the thalamus or pallidum AIs between medicated and unmedicated subjects (uncorrected \(p > 0.20\)), nor with respect to current anxiety or depression comorbidity (\(p > 0.20\)), or age at disease onset or disease duration (\(p > 0.05\)). In terms of OCD symptom, the pallidum AI showed significant association with two of the 5 major Y-BOCS symptom components: hoarding (\(t = -2.37, p = 0.0065\)) and cleaning/contamination (\(t = -2.29, p = 0.014\)), such that cases with these symptoms had reduced leftward asymmetry of the pallidum compared to cases without these symptoms. No significant associations of symptom severity were observed with the thalamus AI, within the pediatric cases (\(p > 0.10\)).

When repeating the main analysis including age\(^2\) in the model, in case of substantial non-linear effects of age on AIs, all of the Cohen’s \(d\) for the effects of diagnosis remained within 0.005 of their values before having included age\(^2\), and the same two AIs (thalamus volume AI, pallidum volume AI) remained significant after FDR correction. None of the AIs showed significant scanner effects in the pediatric data (\(p > 0.05\)), and the significant effects of diagnosis remained when adding scanner field strength as a predictor variable to the main analysis models (pediatric thalamus volume asymmetry: \(t = 2.81, p = 0.0050, d = 0.19\); pediatric pallidum volume asymmetry: \(t = -3.02, p = 0.0025, d = -0.20\)).

We calculated per-subject ‘typicality scores’ (see Methods), and compared the typicality scores between patients and controls. However, no significant differences were found in the pediatric data for either thickness or surface area asymmetries (\(p > 0.15\)). This analysis might have been sensitive to multi-regional disruptions of laterality that are not consistent in direction, as could conceivably arise from generally increased developmental instability.

**Adult data.**

The results for both subcortical and cortical AIs in the adult data, including the effect size estimates for diagnosis on each AI, are presented in Figure 1 and Tables S5–S7. All effects were subtle (Cohen’s \(d\) between –0.086 and 0.066), and not as strong as found in the pediatric data.

The largest effect in adults was a case-control difference in the AI of global hemispheric surface area \((t = -2.48, p = 0.013, d = -0.086)\), indicating that adult OCD was associated with slightly more rightward overall asymmetry in surface area, compared with controls.
However, this did not survive multiple testing correction when accounting for all regional surface area AI comparisons. Post hoc analyses showed that this difference was mainly due to relatively smaller surface area in the left hemisphere (Left: \( t = -2.80, p = 0.0051, d = -0.098 \); Right: \( t = -2.18, p = 0.029, d = -0.076 \)) in adult OCD patients than controls. The effect on this AI remained after excluding potential outliers (see Methods) (\( t = -3.03, p = 0.0025, d = -0.10 \)). No significant case-control difference in the total average asymmetry of cortical thickness was found (\( p = 0.35 \)). No significant differences were found in regional asymmetries after multiple testing correction (Supplementary Materials).

Although the observed effect of diagnosis on the AI of global hemispheric surface area did not survive multiple testing correction, we were interested to explore associations of this AI with case-only variables, as it is a global rather than regional measure. Within the adult OCD patients, there was a trend towards unmedicated cases showing a mean AI difference compared to medicated cases (\( t = -1.77, p = 0.077, d = -0.086 \); i.e., more rightward asymmetry in medicated cases). Adult cases with current depression showed a mean AI difference compared to those without (\( t = -2.15, p = 0.032, d = -0.17 \); i.e., more rightward asymmetry in cases with current depression), while no effect of current anxiety comorbidity was observed (\( p = 0.48 \)). There was no correlation of this AI with the age at disease onset (\( t < 1.0, p = 0.53 \)) or the disease duration (\( t = -1.03, p = 0.30 \)). In terms of OCD severity measures, no significant associations were found with either the severity in total score or the subcomponent variables (\( p > 0.10 \)).

Including age\(^2\) or scanner field strength did not change the main results (Supplementary Materials). Typicality scores (see Methods) showed no case-control differences in the adult data, for either thickness or surface area asymmetry (\( p > 0.15 \)).

The effect sizes of the AI case-control differences in the pediatric and adult data were found to be uncorrelated across the 34 cortical regions, for either thickness AIs or surface area AIs (\( p > 0.40 \)).

**Discussion**

In this study we aimed to map differences in brain asymmetry between OCD patients and healthy controls, by leveraging a collection of 16 pediatric datasets and 30 adult datasets, via the ENIGMA Consortium. Using by far the largest sample size to address this issue to date, the results revealed a small number of asymmetry differences in OCD patients. The largest effects were in the pediatric patients for the volume asymmetry of the thalamus and the pallidum. These effects both had Cohen’s \( d \)-values of around 0.2, which indicates their subtlety and suggests that altered structural brain asymmetry alone is unlikely to be a clinically useful predictor of OCD. Nonetheless, these effect sizes were comparable to those reported by previous large-scale studies of disorder-related changes in brain structure, in which asymmetry was not studied, including studies of OCD as well as major depression, schizophrenia, and autism (e.g., (38, 39, 47–51)). Given that the effect sizes in the present study were estimated based on large sample sizes, relatively accurate estimations of the true effects were possible, whether they were statistically significant or not. As such, the effects are informative to share with the field.
Our finding of subtle changes in thalamus asymmetry in pediatric patients is broadly in accordance with previous disease models for OCD as regards the cortico-striato-thalamo-cortical (CSTC) circuitry, which is involved in a wide range of cognitive, motivational and emotional processes (44). Boedhoe et al. (39) observed a mean increase in bilateral thalamus volume (left plus right) in pediatric OCD patients versus controls, while in the present study, with a larger collection of 16 datasets (including 10 datasets used by Boedhoe et al.), we found that this OCD-related volume alteration was largely left-lateralized and resulted in altered thalamus asymmetry. It is not clear what pathophysiological mechanisms might link altered thalamus asymmetry to OCD. Within OCD individuals, we found no associations of thalamus asymmetry with medication status, age at a disease onset, disease duration, current anxiety and depression comorbidity, or disease symptoms, which might have given some insights into the observed differences. The thalamus is involved in diverse interactions among cortical, subcortical, and brainstem nuclei, and many of its functions are asymmetrical in normal subjects (52). In addition, the thalamus is divided into cytoarchitectonically distinct nuclei with different functions (53). Future studies using higher resolution mapping of internal thalamus subsegments’ structure and function may therefore be informative in pediatric OCD.

For the pallidum, no total volume change (left plus right) was reported by Boedhoe et al. in pediatric OCD patients, while here, with a larger collection of 16 pediatric datasets (including 10 used by Boedhoe et al.), we found an asymmetry difference of the pallidum which was largely driven by a significantly reduced left-sided volume in pediatric OCD patients. Boedhoe et al. also reported that adult OCD patients showed a larger pallidum (again left plus right) than controls, driven by patients with a childhood-onset of disease (39). We saw no significant effect on pallidum asymmetry in adult patients, in either the subgroups of early- or late-onset of disease (Supplemental Materials). This overall pattern of results suggests that disease chronicity, cumulative treatment effects and/or late adolescent volumetric changes in patients are linked to a bilateral increase in pallidum volume, but that reduced left sided volume in pediatric patients reflects a different, earlier developmental process. Moreover, pallidum asymmetry in the pediatric patients showed associations with symptom components “hoarding” and “cleaning/contamination”. Although recently “hoarding disorder” was suggested as a separate diagnostic entity (54), in the present data there was only 1 case with hoarding behavior in the absence of other symptoms. Thus, we do not consider this tentative effect on asymmetry to relate to hoarding disorder specifically.

The pallidum, linking with the striatum and the thalamus within the CSTC circuitry (44), has roles in reward and motivation, as well as broader cognitive, affective and sensorimotor processes (44, 55). Further studies on specific functions of the (left) pallidum in compulsive symptoms, cleaning/contamination behaviors specifically, are needed. While it is not clear why lateralized changes in particular should be involved, in general terms our findings in pediatric cases help to characterize the brain structural changes in this disorder, and suggest altered subcortical neurodevelopment affecting the cortico-striato-thalamo-cortical circuitry. Further research will be needed to clarify any potential functional relevance of asymmetrical alterations in particular.
In terms of cortical measures in the pediatric data, we found no significant case-control differences in the asymmetry of regional or global measures of cortical thickness or surface area. This indicates that none of the cortical case-control differences reported by the previous large-scale ENIGMA study (38) are significantly lateralized, even when they might have been reported with respect to only one side. We also used a multivariable measure to describe the ‘typicality’ of each subject’s asymmetry pattern over all cortical regions with respect to a healthy and general population database (40). However, no case-control differences in this measure were found. Together these analyses indicate that alterations of cerebral cortical anatomical asymmetry are not notable features of pediatric OCD.

In the adult data, there was no evidence for case-control differences of regional asymmetries, for either subcortical or cortical measures. The strongest cortical effect in adults was at the total hemispheric level, whereby cases showed slightly more rightward asymmetry of total surface area, mainly due to having a relatively smaller surface area in the left hemisphere than controls. However, this very small effect, with Cohen’s $d$ of 0.086, was not significant in the context of multiple testing, so that further studies with even larger sample sizes will be needed to confirm or refute this result. The effect was more pronounced in cases with comorbid depression, although this observation also remains tentative in the context of multiple testing.

Consistently with the previous findings of distinct alterations between pediatric and adult patients by the ENIGMA OCD Working Group (38, 39), the present study of structural asymmetry also showed different OCD-related effects between pediatric and adult data. There was also no correlation of case-control asymmetry differences between pediatric and adult data across the 34 cortical regions, which further supported the distinct OCD-related effects between pediatric and adult patients. Nonetheless, it is intriguing that the most notable effects in the pediatric and adult data all involved predominantly left-hemisphere alterations, which might support previous models of left-hemisphere dysfunction in OCD, as have been suggested by some functional imaging and neuropsychological findings (see Introduction) (23, 27–29). However, it will be important for future functional imaging studies to avoid reporting lateralized dysfunction on the basis that only one of the two hemispheres shows significant case-control differences. This is because, as noted in the Introduction, a hemispheric difference of significance does not necessarily indicate a significant difference of effects between hemispheres.

OCD is a heterogeneous neuropsychiatric condition with a heritability of roughly 40%, as has been observed using both twin/family based estimation and SNP-based estimation (5, 56). A recent study showed that genetic variation across the genome, which impacts risk for OCD, also includes variation which affects the volumes of the nucleus accumbens and putamen (57). The structural brain asymmetries which showed the strongest associations with OCD in the present study have been shown to have significant heritability: 23% for the volume asymmetry of the thalamus, 15% for the volume asymmetry of the pallidum (43), and 17% for the total hemispheric asymmetry of cerebral cortical surface area (40). It may therefore be useful in future studies to assess the genetic correlation between these aspects of brain asymmetry and OCD, which might lead towards genome-wide association studies.
(58) to identify individual genetic loci that are involved in OCD-related asymmetry abnormalities.

This study has several limitations. First, the cross-sectional study design limits the interpretation of the results particularly with respect to age-related changes. Further work using longitudinal studies, and incorporating genetic and environmental variables, may be useful to understand the mechanisms underlying the potential associations reported here. Second, while the region-based approach used in this study is feasible for large-scale, collaborative projects, it is necessarily limited in terms of spatial resolution, and this might have contributed to some of the null results for regional cortical or subcortical regions. Investigation with more fined definition of regions (e.g., sub-regions of the thalamus (59)) or a vertex-wise approach combined with cross-hemispheric registration methods will be likely to be useful for future cortical asymmetry studies (60, 61). Third, the symptoms of OCD are heterogeneous (4). Identifying potential subtypes of OCD could therefore provide further insights into the pathophysiology.

In summary, we mapped structural brain asymmetry in pediatric and adult OCD as compared to controls, using by far the largest sample size to date. Effects were small overall, and most pronounced in the thalamus and the pallidum in pediatric patients, which also showed potential links with medication status, disorder severity, and/or anxiety and depression comorbidities. Our study adds to literature implicating the thalamus in the pathophysiology of pediatric OCD, and additionally implicates the pallidum in pediatric cases. The full set of results from this study is available in the SI Tables and online for easy access (https://conxz.github.io/AsymOCD/).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References


Highlights:

Brain structural asymmetry alterations in patients with OCD were investigated.  
This study was performed with a large sample size via the ENIGMA Consortium.  
The largest case-control mean differences were found in the thalamus and pallidum in pediatric OCD patients.  
Alterations of structural asymmetry in OCD were subtle and restricted to pediatric cases.
In terms of cortical asymmetries in the pediatric data, no significant case-control differences in the global hemispheric AI for either cortical thickness or surface area were found ($p_s > 0.40$). Regionally, only one AI showed a nominally significant effect (i.e. prior to multiple testing correction) of diagnosis, which was for thickness asymmetry of the lateral occipital cortex (greater rightward asymmetry in OCD patients; $t = -2.08, p = 0.038, d = -0.14$; Figure 2). This did not survive multiple testing correction. No other AIs in case-control comparisons within the pediatric data showed significant effects (uncorrected $p_s > 0.05$).
Figure 2. Subcortical structures showing altered volumetric asymmetry in pediatric OCD patients: the thalamus and the pallidum.

The violin plots show the distributions and group differences of the volume asymmetry (A) and the lateral volume measures (in mm$^3$) in each hemisphere (B) for the thalamus and the pallidum. Note that the main analyses were based on linear mixed-effect modelling with ‘dataset’ as a random-effect term, whereas data are plotted here without correction for the ‘dataset’ variable, for display purposes only.
Table 1.
Summary information on the case-control datasets included in the present study.

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**Adult Samples Combined**

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Site indicate the representative author of each dataset; Numbers in parenthesis indicate the standard deviation of age.